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in a thirteen weeks' course and the incidence of jaundice was from 7 to 8 per cent. After 1937 the dosage was increased to 13 grammes in thirteen weeks and the jaundice rate was from 25 to 30 per cent. Reducing the amount of arsenic by the use of Mapharside appears to reduce the incidence of jaundice.

I have records of ten patients treated with neoarsphenamine in doses of only 0.45 gramme weekly but they did not develop jaundice at the critical period. As their treatment is not yet complete, this finding is inconclusive.

Summary

The present increase in jaundice as a complication of the arsenical treatment of syphilis is coincident with an increase of infective hepatitis in the general population, but people under treatment for syphilis are much more apt to be affected.

The same clinical types can be observed in cases in which arsenical treatment has been given, and also in those patients who have not been given any treatment. As yet obvious pathological distinctions cannot be made. There are five factors which possibly increase the liability to liver damage in syphilitics.

(1) The use of arsenic in treatment. The fact that the bulk of cases of jaundice occur at about the same time in the course of treatment may suggest that a threshold amount of an arsenical drug is necessary to produce damage.

(2) Syphilis itself.

(3) Environment. Some people may live in conditions which are more conducive to the spread of an infection, if this is a factor.

(4) Diet. The absence of some constituent of the diet, particularly in war-time, may reduce the resistance of the liver.

(5) Sex. Males are infinitely more liable to jaundice than females.

With regard to the essential cause of jaundice, our present evidence suggests that the liver has only one way of reacting to a variety of infecting or toxic agents.

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JAUNDICE IN SYPHILITICS*

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I do not intend to deal with the whole question of syphilitic jaundice, but will confine myself to cases of jaundice due to, or concurrent with, treatment by the arsphenamines.

Although infective hepatitis or catarrhal jaundice is occurring in epidemic form in various parts of Great Britain, I have been unable to obtain evidence of an incidence among non-syphilitic men in the Forces in Scotland even remotely approaching the percentage I have encountered among members of the Forces undergoing antisyphilitic treatment.

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It is possible that for every case of clinical catarrhal jaundice there are numerous cases of subclinical infective hepatitis demonstrating only some minor febrile or gastro-intestinal upset without jaundice. Such subclinical infections may be activated by arsphenamine treatment or may damage the liver to a degree rendering it more susceptible to the arsphenamines. Recent work has shown that some impairment of liver function, as shown by the bilirubin test, may be demonstrated for periods up to two years after an attack of catarrhal jaundice. The thesis that an infective agent is present is strongly supported by the fact that some reduction in the incidence of jaundice has been obtained by the prevention of overcrowding in V.D. departments and by greater care in the avoidance of transfer of any possibly infected materials such as blood by syringes. It is my belief, however, that there still remains an *x* factor, as Colonel L. W. Harrison has called it, the unknown or unproven factor or factors in the problem of arsphenamine jaundice.

One feature which is notable in many cases of post-arsphenamine jaundice is the absence of febrile reaction or constitutional signs and symptoms, other than nausea and anorexia, as opposed to an obvious constitutional upset before the onset in other forms of jaundice.

Toxicity of drugs

The actual toxicity of the drug has been excluded so often as the only factor that I think it can be left out of our consideration for the moment, but since Frei's work in 1928 the question of the sensitizing effect of the neoarsphenamines has been raised by many investigators. Even as regards the actual toxicity, however, there may be variables which are not generally taken into account. Nedzel (1942) concluded from experiments with rabbits and white rats that the toxic effects of neoarsphenamine are more severe when the temperature is low and the barometric pressure high or when there is an abrupt fall of barometric pressure or temperature, such factors applying in the case of both immediate and of delayed deaths. Although animal experiments cannot be taken as directly referable to man, such experimental observations may one day prove of value.

Sensitization

In the case of cutaneous hypersensitivity in guinea-pigs to neoarsphenamine Sulzberger and Mayer (1931) showed that there were regional and seasonal variations and striking differences between the results obtained in one place, on green (summer) food and dry (winter) diet, the green (alkaline ash) inhibiting sensitization, the dry favouring it; they considered that the difference related to the acid-base balance rather than to vitamins.

In later work on similar lines Sulzberger and Simon (1934) proved that the variations were not racial or constitutional (vide transfer of refractory New York animals to Boston, where they became just as easily sensitized by the same technique, brand and water as the indigenous animals) and they concluded that hypersensitivity is apparently specific to the arsenobenzol complex, that different lots of "914" may vary in their sensitizing proclivities and that the "sensitization index" is apparently independent of the actual toxicity. Some pathologists hold that the liver damage from the arsphenamines is also a question of sensitization, as are the blood dyscrasias which occur as sequelae from the arsphenamines or related aromatic substances.

Diet

Other experimental work has emphasized the effect of diet in protection of the liver in the case of certain drugs. Messinger and Hawkins (1940), working with dogs, showed that protein diet is the best protector against liver damage by big doses of arsphenamine and that a fat diet is deleterious and may, if substituted for protein or carbohydrate, produce recurrence of jaundice without further administration of arsphenamine. Miller and Whipple (1940) and Miller, Ross and Whipple (1940) working with chloroform in dogs,

showed that liver injury increases in extent as the body stores of protein-forming material are depleted and suggest that carbohydrate acts indirectly as a "protein-sparer at the source."

The importance of protein, especially of the sulphur-containing amino-acids, in the health of the liver cell is now generally recognized, and Messinger and Hawkins were able to give protection against arsphenamine by administration of methionine. Longley and Miller (1942) showed in animals that there was little change in urea clearance with additions of protein beyond 40 grammes but there was a progressive increase in clearance and of fasting protein nitrogen up to this point. Whipple (1942) states that normally there is a reserve of plasma protein-forming material one to five times the circulating mass, which reserve may be reduced by fasting, by low protein diet or by plasma depletion.

Incidence

I am not aware of the exact incidence of jaundice in Great Britain, but I have been told that in certain civil V.D. clinics the incidence of jaundice occurring during neoarsphenamine treatment has risen in a manner analogous to that of my own experience in the Forces. There is overcrowding among the civil populace as there is in the Forces, but I have been unable to obtain evidence of the occurrence of epidemics (even minor) of jaundice in non-syphilitics in the units to which the syphilitic jaundice patients belonged. The latter have not been found in certain units only but, so far as my experience goes, they have been single cases in many units.

During the period 1st July to 31st December, 1942, among 1,659 cases of syphilis under treatment among the Forces in Scotland, 171 cases of jaundice (including two fatal) were recorded, giving a percentage of 10.3. There did not appear to be any seasonal variation of great note in the incidence of jaundice, the numbers recorded by months varying only from twenty in July and November to thirty-nine recorded in August: actually the greatest numbers recorded occurred in the three months August to October, during which 108 out of the 171 cases were recorded.

Infective v. obstructive jaundice

In a small series (twenty-one cases), along with icteric index and van den Bergh readings, estimations of the plasma cholesterol and plasma phosphatase were carried out to see whether all the cases belonged to the toxic infective group as opposed to those of obstructive jaundice and whether or not any noticeable increase of phosphatase was present, as arsenical jaundice is stated to be peculiar among toxic forms in giving readings approaching those found in obstructive types. In only five cases (the patients had received amounts varying from 4.40 grammes to 16.95 grammes of neoarsphenamine prior to the onset of jaundice) were the readings at all suggestive. In these five cases, whereas the icteric indices were only from 2 to 24 units and the van den Bergh readings from 0 to 16 units (8 milligrams of bilirubin), the plasma cholesterol readings were on the low side, varying from 93 to 138 milligrams per cent, and the plasma phosphatase was raised, the estimation varying from 21 to 32 King-Armstrong units per cent in place of the normal 6 to 13 units per cent. The most significant case was the one in which the patient had received 16.95 grammes of neoarsphenamine; only faint bile staining remained; the icteric index was 2 units and the van den Bergh 0.8 units; the plasma cholesterol was 113 milligrams per cent and the plasma phosphatase 22 units per cent. Taking the series generally, however, it could not be said that any clear-cut dividing line could be made out which would differentiate "arsenical" jaundice from jaundice due to other toxic infective causes.

Detection of potential jaundice

The possibility of detecting the potential jaundice case before jaundice develops would be of inestimable value and in routine clinic practice testing of the urine for excess of urobilinogen by Ehrlich's reagent is, in my opinion, the most valuable

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side-room method, but estimation of the liver's ability to stand up to treatment would be much more valuable. In consultation with Professor J. W. McNee and Dr. J. B. Rennie it was decided to carry out a series of liver efficiency tests by Quick's method, as being the most reliable test of the detoxicating function of the liver. The tests were done by Quick's method of oral administration of 6 grammes of sodium benzoate and subsequent estimation of the hippuric acid excretion. Although the work is yet by no means complete and fully assessable, the preliminary results may be of some interest.

Results of Tests.—Tests carried out in 346 cases, including ninety-three cases of jaundice, gave results from 0 gramme to 5.5 grammes of hippuric acid excreted, the lower readings being found, naturally, in the jaundice cases. I am indebted to Lieutenant Colonel G. L. Montgomery, A.D.P., Scottish Command, and to Major R. Riddle for most of these estimations.

In 129 cases, prior to the administration of any arsenicals, the results varied from 1.8 grammes to 5.5 grammes, the great majority giving results of 3 grammes and upwards: in ten of these cases, in which initial readings had been from 2.7 to 4.7 grammes (with drop to readings between 1.6 and 3.4 grammes on further tests during treatment) the patients subsequently developed jaundice. A patient whose initial excretion was 1.8 grammes was given an injection of 0.30 gramme of neoarsphenamine and the test was then repeated; as the second test result was 0.5 gramme administration of neoarsphenamine was suspended for the time being.

In ninety-five cases, in which the patients had received previously various amounts of arsenicals, the range of the results was from 1 gramme to 4.9 grammes, but the general level was somewhat lower than in the previous series. Of these patients nineteen were already jaundiced when first tested or subsequently developed jaundice; their excretions were from 1 gramme to 3.6 grammes and in one case the patient excreted 4.4 grammes initially, before the excretion figure fell with the onset of jaundice.

Although these preliminary findings do not appear to give any definite guide in the initial tests, prior to administration of the arsenicals, it is my feeling that any reading below 3 grammes during antisyphilitic treatment is an indication for caution. I think time will prove this test of value, but the possibility of over-frequent administration of sodium benzoate causing damage to the liver on its own cannot be ignored.

Synchronized tests.—To exclude the possibility that some patients might have a considerable diminution of protein reserves through pronounced physical strain or plasma depletion a series of estimations of plasma proteins was carried out synchronously with the liver function tests, but, as was expected, a departure from the normal was not found—diminution of the circulating protein is scarcely to be expected except in extreme depletion of the protein reserves. The albumen-globulin ratio remained normal.

In an attempt to determine whether or not substitution of arsenoxide for the aromatic trivalent arsenicals would reduce the incidence of jaundice the patients in a series of cases were treated with Mapharside. In fifty-nine cases there have been, to date, four cases of jaundice, or 6.8 per cent, but of the four cases of jaundice one was a definitely febrile infective hepatitis occurring at the beginning of the course, with "influenza" symptoms preceding the jaundice, and two had been given neoarsphenamine during the course at other centres (in fact one patient received what was practically a course of neoarsphenamine after a few doses of Mapharside).

Reduction of dosage of neoarsphenamine has so far produced only a slight reduction in the number of cases of jaundice occurring in Scotland among patients receiving antisyphilitic treatment.

In two fatal cases necropsy showed the extreme central necrosis characteristic of such livers, with some bile-duct regeneration.

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Increased incidence in Germany

In spite of my negative contribution there is one fact from which I take consolation (albeit also a negative one) and that is that we are not alone in having trouble with arsenical jaundice, for Stumpke (1942) stated last year that, just as in the war of 1914-18, there has been an increase in toxic reactions after arsphenamine injections in Germany: he suggests (a) an increase in virulence of the disease and (b) malnutrition as causes.

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DISCUSSION

Professor John Beattie drew attention to the work of Whipple and his co-workers on the power of sulphur-containing amino-acids to protect the liver from damage caused by the administration of chloroform and other like substances. Whipple's results indicated that when the amount of such amino-acids in the diet was increased, the liver damage was averted. Although the distribution of the cellular damage within the liver was not identical with that found in cases of jaundice described by other workers, the actual cellular changes seemed to be identical.

Whatever the aetiological factors concerned with the dysfunction, disorganization and necrosis of the liver cell in the jaundice of syphilitics, the liver cell is certainly the point of attack. It seemed reasonable, therefore, to attempt to prevent the liver damage by increasing the amount of sulphur-containing amino-acids in the diet during the fourteenth and fifteenth weeks after arsenical treatment has been begun. With the cooperation of Major Marshall, a series of experiments is being carried out, with suitable controls, on the effects of administering known amounts of these substances. So far it is not possible to form an opinion, as only one group of patients has been treated. In this group, the increase in the sulphur-containing amino-acids amounted to only 20 to 25 per cent, and significant differences in the incidence or severity of the jaundice has not been noted. The second and later groups are being given greater amounts over the same and longer periods of time. When these groups are studied, it will be possible to arrive at an opinion as to the usefulness of this method of prophylactic treatment.

Professor R. A. Peters said that judging from the abstract point of view, it seemed to him that the point concerning dietary which had been made by Professor Beattie and others was the first thing to which they should direct their attention. It was likely to be nearer the mark than anything else. He also asked whether or not, in cases of arsenical jaundice, any estimations had been made of the actual arsenical content of the tissues.

Col. H. B. F. Dixon said his experiences of jaundice were in three phases. First, as a physician for many years before the present war, he had seen what was called catarrhal jaundice which occurred sporadically every year in the British Army, both at home and abroad; there were usually about 800 to 1,000 cases each year. Usually there was never more than one or two cases in the wards, and on the whole it was mild, although some cases looked like sand-fly fever at the beginning, until the jaundice appeared. The second phase was in Malta in 1938 to 1942, when he had seen about 600 cases of what is now known as infective hepatitis which was considered to be a virus infection with a long incubation period. Although there were a number of patients with syphilis receiving treatment he only saw one or two patients with jaundice after arsenical treatment, and it never struck him that the condition was due to the arsenic. About 50 per cent of the cases were febrile and it was confined to British troops. The third phase was at the Connaught Hospital which receives from the South East of England all patients with jaundice after antisyphilitic treatment and also all the patients in the area with infective hepatitis and who have not had antisyphilitic treatment. In 1942, 157 patients had been admitted of which 108 had received antisyphilitic treatment some time within the previous eighteen months: clinically there was not any difference between the two groups and the patients in each group took the same time to recover.